UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,144	09/27/2004	Kurt Berlin	P098US	6722

93734 7590 09/21/2010

Epigenomics AG
Kleine Praesidentenstr. 1
Berlin, 10178
GERMANY

EXAMINER	
POHNERT, STEVEN C	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
09/21/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ip@epigenomics.com
ramin.amirsehhi@epigenomics.com
armin.dorner@epigenomics.com

Office Action Summary	Application No.	Applicant(s)	
	10/509,144	BERLIN, KURT	
	Examiner	Art Unit	
	STEVEN C. POHNERT	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *12-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claim Status and formal Matters

Claims 1-15 are pending.

Claims 12-15 are withdrawn.

Claim 1 has been amended.

The previous grounds of rejection have been withdrawn in view of the declaration by Dr. Berlin.

This action is non-final as it contains new grounds of rejection not necessitated by amendment.

The instant response is non-compliant. Claims 12-15 are listed as previously withdrawn.

Response to Amendment

1. The Declaration under 37 CFR 1.132 filed 5/7/2010 is sufficient to overcome the rejection of claims 1-11 based upon Berlin et al as it has demonstrated that the Art of Berlin is not by others.

Priority

The instant application was filed on 9/27/2004 as a National Stage entry of PCT/EP03/03104 filed 3/25/2003 and claims priority to German Application 102 14 232.7 filed 3/25/2002.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-6, 9, and 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010) and Oakley et al (Pharmacology & Therapeutics (1999) volume 84, pages 389-400).

Genomic methylation pattern is interpreted to include tissue specific methylation patterns.

The amendment to the claims to recite hemimethylation requires the presence of a methylated and non-methylated strands.

The amendment of "said DNA being methylated at one or more cytosine positions" is not defined in the specification. Thus "said DNA being methylated at one or more cytosine positions" is being given the broadest reasonable interpretation of a single or double stranded DNA with at least one cytosine that is methylated.

Lopez et al teaches the amplification of genomic DNA by PCR in the presence of a DNA methyltransferase (see figure 1and page 17, lines 26-28) (claim 1) and amplification by single strand displacement amplification and methylation with a DNA methyltransferase (see page 18, line 10-16) for detection. PCR and single strand displacement amplification are interpreted as steps b-C of claim 1. The strands synthesized by chain extension or single strand displacement contain the methylated parent strand and synthesized strand, which is not methylated and thus are hemimethylated. Lopez teaches ^{3}H-s-adenosyl methionine as a methyl donor with a

detectable label (see page 4, line 2) (claim 4 and 5). Lopez et al further teaches the use of anchored PCR primers on a solid matrix to create ordered maps (see page 21 lines 2-4) (claim 6). Lopez et al teaches the treatment of amplified targets with methylation sensitive restriction enzyme capable of distinguishing methylated and non-methylated cytosines (see page 32, lines 25-29).

Lopez et al does not teach the use of DNA methyltransferase that preserves methylation status of genomic DNA, providing a sample DNA with one or more methylated cytosines (claim1). Lopez does not specifically teach analyzing the methylation status to determine the methylation status of the starting sample (claim 1, step g).

Lopez et al does not teach the use of DNMT1 a maintenance methyltransferase (claims 2 and 3). However, Pradhan et al teaches the use of DNMT1 as a methyltransferase (see abstract). Pradhan teaches maintenance methylation "ensures propagation of tissue specific methylation patterns during development" (see page 33002, first column text, lines 8-10). Pradhan teaches that DNMT1 has a higher reaction velocity for hemimethylated DNA substrates (see page 3302, 2nd column, last paragraph). Pradhan thus teaches DNMT1 is a maintenance methyltransferase ensures propagation of specific methylation patterns. Pradhan further teaches cytosine methylation is important in embryonic development, carcinogenesis and genetic disease (see page 33002, 1st column of text lines 1-5). Pradhan thus teaches maintenance methylation and the methyltransferases that maintain methylation patterns are important

in embryonic development, carcinogenesis and genetic disease. Pradhan teaches the use of DNA known to be methylated (page 33006, 2nd column, last paragraph).

Oakley teaches that 5-methyl cytosine is the most frequent modification found in Eukaryotic genomes (389). Oakley teaches that four types of methylation occur in the nucleus, including maintenance methylation of hemimethylated sites (390). Oakley teaches that methylation plays a role in host defense against molecular parasites and the regulation of transcription (390). Oakley teaches numerous methods of detecting methylation status of a genomic sequence including the use of a bisulphite solution.

Therefore it would have prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the DNMT1 methyltransferase taught by Pradhan as the methyltransferase in Lopez's method of amplification and methylation of eukaryotic genomic DNA because Pradhan teaches DNMT1 is a maintenance methyltransferase that ensures propagation of methylation patterns. It would have been further prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the amplified DNA with the genomic methylation pattern generated by the combination of Pradhan and Lopez in the methods of detecting methylation taught by Oakley. The ordinary artisan would be motivated to use the DNMT1 of Pradhan with Lopez method of Pradhan's method of methylating and amplifying DNA because it would for the production of larger quantities of methylated DNA with the genomic methylation pattern. The artisan would be motivated to analyze the amplified DNA with the genomic methylation produced by the method of Lopez and Pradhan in the methods of Oakley, because it would allow for detection of methylation patterns and thus further

understanding of genomic imprinting, transcriptional regulation and tumorigenesis as taught by Oakley and Pradhan. The artisan would have a reasonable expectation of success as they are merely replacing a one methyltransferase for another in methods of amplifying and methylating DNA and using known methods of detecting methylation.

Response to Arguments

This is a new grounds of rejection. The response provides no arguments to the instant rejection as the teachings of Berlin are no longer relied upon.

4. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010) and Oakley et al (Pharmacology & Therapeutics (1999) volume 84, pages 389-400) as applied to claims 1-6, 9, and 10-11 above, and further in view of Shatkin et al (US Patent 6312926).

The teachings of Lopez, Pradhan and Oakley are set forth above. Lopez, Pradhan and Oakley do not teach the methyltransferase immobilized on a solid support.

However, Shatkin et al teaches the use of hMET (methyl transferase) immobilized on protein G beads for washing assays (see column 24, lines 3-12).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Lopez, Pradhan and Oakley method of amplifying genomic DNA while maintaining genomic methylation patterns with immobilized methyltransferase taught by Shatkin, because Shatkin teaches immobilization allows washing of assays. The ordinary artisan would be motivated to improve Lopez, Pradhan and Oakley method of amplifying genomic DNA while maintaining genomic methylation patterns with immobilized methyltransferase or

polymerases as taught by Shatkin, because Shatkin teaches immobilization allows washing of assay and detection of protein interactions.

Response to Arguments

This is a new grounds of rejection. The response provides no arguments to the instant rejection as the teachings of Berlin are no longer relied upon.

5. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lopez et al (WO/1999/10540) in view of Pradhan, et al (Journal of Biological Chemistry (1999) volume 274, pages 33002-33010) and Oakley et al (Pharmacology & Therapeutics (1999) volume 84, pages 389-400) as applied to claims 1-6, 9, and 10-11 above, and further in view of Stemple et al (WO/2000/53805).

The teachings of Lopez, Pradhan and Oakley are set forth above. Lopez, Pradhan and Oakley do not teach the polymerase immobilized on a solid support.

However, Stemple teaches the immobilization of a polymerase on a solid support (see page 3 lines 14-15). Stemple teaches immobilization or fixing the site of the polymerase allows assaying of multiple nucleic acids simultaneously (See page 7, lines 25-26).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve Lopez, Pradhan and Oakley method of amplifying genomic DNA while maintaining genomic methylation patterns with immobilizing a polymerases as taught by Stemple, because Stemple teaches immobilization or fixing the site of the polymerase allows assaying of multiple nucleic acids simultaneously. The ordinary artisan would be motivated to improve Lopez, Pradhan and Oakley method of amplifying genomic DNA while maintaining genomic

methylation patterns with immobilized polymerases as taught by Stemple, because Stemple teaches immobilization or fixing the site of the polymerase allows assaying of multiple nucleic acids simultaneously.

Response to Arguments

This is a new grounds of rejection. The response provides no arguments to the instant rejection as the teachings of Berlin are no longer relied upon.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 1-5 and 9-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11-12 and 15 of copending Application No. 11/904,320 in view of Allis (WO02/18418 published 3/7/2002) and Oakley et al (Pharmacology & Therapeutics (1999) volume 84, pages 389-400).

This is a provisional obviousness-type double patenting rejection.

Instant claims 1-5 are drawn to a method of cytosine methylation analysis by providing a template DNA, heating the template DNA, cooling the template DNA in the presence of primers, heating the DNA in the presence of a polymerase, contacting the hemimethyalted DNA in the presence of a methyl transferase and a methyl done to result in the methylation of the corresponding CpG and repeating the steps a plurality of time before analyzing the sample. Claim 11 of '320 is drawn to converting a genomic DNA by a copying reaction (primer extension of pending claims), treating the sample with a methyl transferase specific for hemimethylated DNA using s-adenosylmethionine and detecting the presence of the s-adenosyl methionine. Claim 12 of '320 is draw generating a hemimethyalted double stranded DNA by heating and annealing DNA samples, labeling hemimethylated double stranded using DNMT1 and a labeled s-adenosylmethionine and analyzing the sample.

The claims of '320 do not specifically teach or suggest repeating the steps.

However, Allis teaches, "a mechanism for replicating methylated CpG dinucleotides exists: maintenance DNA methyl transferase (DNMTs) recognize hemimethylated DNA (DNA methylated on only one strand) and add methyl groups to the cytosine residues on the complementary strand." (page 36, lines 20-27).

Oakley teaches that 5-methyl cytosine is the most frequent modification found in Eukaryotic genomes (389). Oakley teaches that four types of methylation occur in the nucleus, including maintenance methylation of hemimethylated sites (390). Oakley teaches that methylation plays a role in host defense against molecular parasites and

the regulation of transcription (390). Oakley teaches numerous methods of detecting methylation status of a genomic sequence including the use of bisulphite solutions.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to repeat the process of the claims of '320 to produce a plurality of nucleic acids to allow sufficient quantities to improve reliability of the assays as taught by Oakely in view of the teachings of Allis and Oakley. The artisan would have a reasonable expectation of success as the artisan is using known methods in a manner suggested by the art.

Response to Arguments

The response asserts it would like to postpone dealing with the rejection until the rejection is no longer provisional.

Summary

No claims are allowed.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C. POHNERT whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Steven C Pohnert/
Primary Examiner, Art Unit 1634